NIH RELAIS Document Delivery

NIH-10126343

NIH -- W1 AN62L

PAMELA GEHRON ROBEY
CSDB/NIDR/NIH Bldng 30 Rm 228
30 CONVENT DRIVE MSC 4320
BETHESDA, MD 20892

ATTN:
PHONE: 301-496-4563
FAX: 301-402-0824
E-MAIL:

SUBMITTED: 2002-02-02 05:22:26
PRINTED: 2002-02-04 16:15:38
REQUEST NO.: NIH-10126343
SENT VIA: LOAN DOC
5769539

NIH Fiche to Paper Journal

TITLE:	ANNALS OF PLASTIC SURGERY
PUBLISHER/PLACE:	Little, Brown And Company Boston Ma
VOLUME/ISSUE/PAGES:	1998 Jul;41(1):75-80 75-80
DATE:	1998
AUTHOR OF ARTICLE:	Szwajkun P; Chen YR; Yeow VK; Breidahl AF
TITLE OF ARTICLE:	The 'Taiwanese giant': hormonal and genetic influe
ISSN:	0148-7043
OTHER NOS/LETTERS:	Library reports holding volume or year
	7805336
	9678473
SOURCE:	PubMed
CALL NUMBER:	W1 AN62L
REQUESTER INFO:	AB424
DELIVERY:	E-mail: probey@DIR.NIDCR.NIH.GOV
REPLY:	Mail:

The "Taiwanese Giant": Hormonal and Genetic Influences in Fibrous Dysplasia

Phillip Szwajkun, MD
Yu-Ray Chen, MD
Vincent Kok Leng Yeow, MBBS, FRCS(Ed), FRCS(Glas)
Alan Frederick Breidahl, MBMS, Dip Anat, FRACS

A 14-year-old boy has been followed for 4 years with a rapidly growing, recurrent area of fibrous dysplasia of the left maxilla and zygoma following resection and bone grafting. Standing 190 cm tall, he was found to have elevated serum growth hormone levels and a pituitary adenoma. His case appears to represent a postzygotic gene mutation of McCune-Albright syndrome. It is possible that the elevated growth hormone levels are in part responsible for the rapid progression of the tumor.

Szwajkun P, Chen Y-R, Yeow VKL, Breidahl AF. The "Taiwanese giant": hormonal and genetic influences in fibrous dysplasia. Ann Plast Surg 1998;41:75–80

From the Chang Gung Craniofacial Center, Chang Gung Memorial Hospital, Taipei, Taiwan.

Received Aug 14, 1995, and in revised form Feb 26, 1998. Accepted for publication Feb 26, 1998.

Address correspondence to Dr Chen, Chang Gung Memorial Hospital, 199 Tung Hwa North Road, Taipei, Taiwan.

Since 1876, the case of the "Tegernsee giant" has been shrouded in mystery and legend. His enormous skeleton (231 cm) with huge bony overgrowth of the skull and mandible has been preserved at the Institute of Pathology at Munich University. Although the association of polyostotic fibrous dysplasia (FD) and juvenile gigantism was reported as early as 1942,[1] the recent identification of a postzygotic gene mutation in multiple tissues of McCune-Albright patients has provided as explanation for this unusual case.[2,3]

In 1994, a 14-year-old boy returned to the Chang Gung Craniofacial Center with a rapid, extensive recurrence of FD that had been resected previously from the maxilla and zygoma, and he had undergone bone graft reconstruction. An endocrinological evaluation for inappropriate height for age (190 cm at 14 years of age) revealed elevated serum growth hormone levels and a pituitary adenoma. We attributed the marked recurrence and unusual invasion of previous bone grafts to elevated levels of growth hormone from the pituitary tumor, similar to the proposed affliction of the "Tegernsee giant." Furthermore, growth hormone excess is an uncommon hormonal factor in polyostotic FD and McCune-Albright syndrome.

Patient Report

A 10-year-old was referred to the Chang Gung Craniofacial Center with left cheek and facial swelling, malocclusion, and mild left proptosis. Evaluation by computed tomography (CT) revealed probable FD, with involvement of the left maxilla, pterygoid, zygoma, clivus, and parietal cranial regions. An ophthalmological examination revealed no visual deficit. There was no other clinical evidence of FD and the ribs were not involved on chest radiograph.

The patient underwent subradical excision of the left maxilla and zygoma with full-thickness and split-thickness rib graft reconstruction. Postoperatively he retained some asymmetry of the orbital region, but had gained a reasonable degree of symmetry in the lower maxillary region (Fig 1). It is our experience that, after radical resection in the craniomaxillofacial region, recurrence rarely if ever affects bone grafts used in the previous reconstruction.[4] In this patient, however, a 4-year follow-up revealed an unusually rapid recurrence with invasion of the bone-grafted reconstructed site (Fig 3).

The patient was also noted to have an unusually rapid growth spurt (10.4 cm in 1 year), with a resultant height of 194 cm. Due to this inappro-

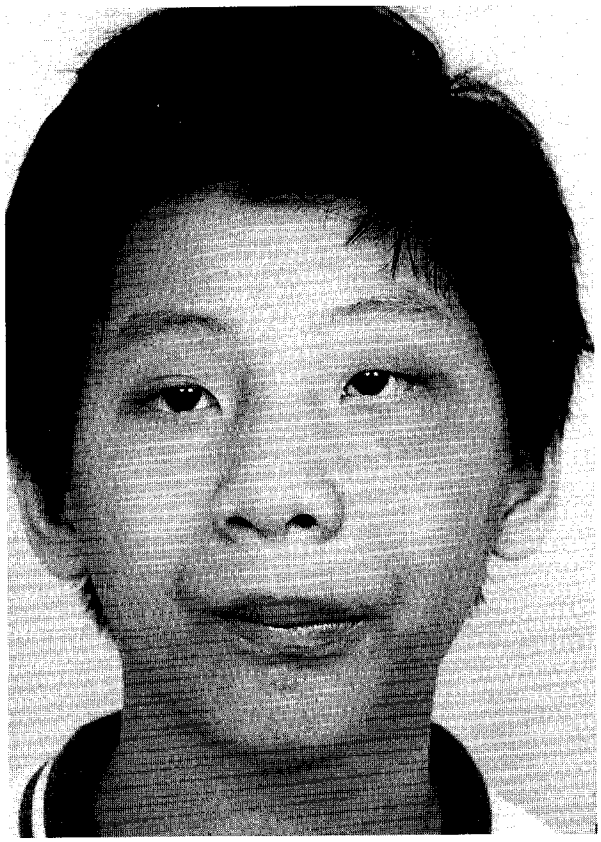

Fig 1. Three months after first resection and rib graft reconstruction of left maxillary fibrous dysplasia.

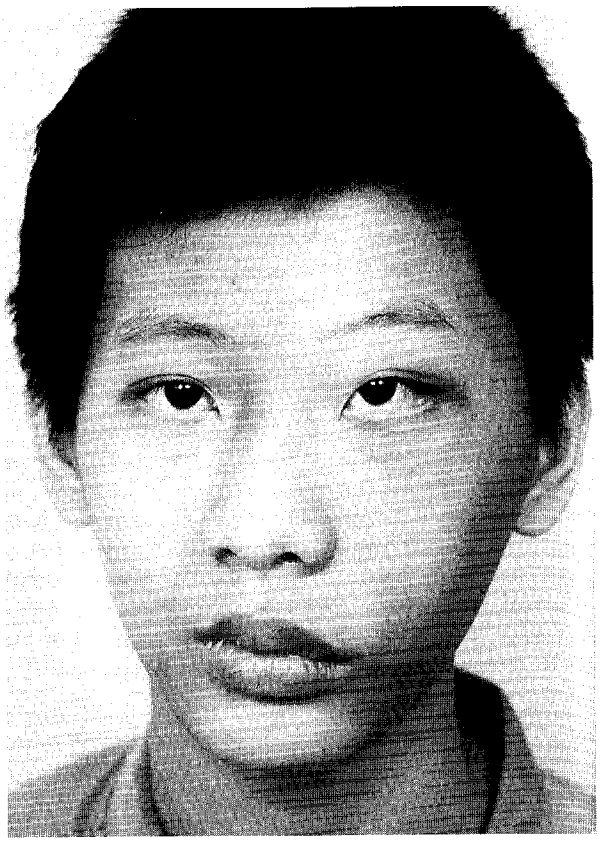

Fig 2. Further aggressive recurrence noted in the 6 months between the second resection and the removal of the pituitary adenoma. Note the gross swelling in the lower maxillary area, despite achieving symmetry here 6 months earlier.

priate height for his age, as well as the unusually aggressive recurrence, an endocrinological evaluation for growth hormonal disturbance was sought. The growth hormone was found to be significantly elevated at 23.7 ng per milliliter (normal: children, <10 ng per milliliter; adults, <5 ng per milliliter). There was no clinical evidence of precocious puberty and the thyroid was only minimally enlarged. Coronal and axial CT of the sella tursica revealed an enlarged nonenhancing pituitary gland with possible pituitary tumor (see Fig 3C).

The patient was started on Sandostatin for temporary control of growth hormone excess. The recurrence of FD was explored surgically and found to have invaded the bone graft. Conservative contour shaving was performed, and histology revealed invasion of the previous rib graft with FD. The patient had an unremarkable postoperative course. Neurosurgical excision of the pituitary tumor 6 months later revealed a large adenoma that had undergone hemorrhagic necrosis. Unfortunately, in this short period, marked recurrence of maxillary FD reoccurred (Figs 2 and 4).

Discussion

FD is an abnormal ingrowth and replacement of normal bone by an irregular trabeculae of variably mineralized fibrous tissue. Monostotic FD is defined as the presence of FD at one site, which may involve contiguous structures. Polyostotic FD affects two or more noncontiguous sites, including the craniomaxillofacial skeleton. Monostotic sites in the craniomaxillofacial skeleton are the calvarium, the base of the skull, the zygoma, the maxilla, and the mandible. If FD was to involve more than one of these sites in any combination, this would then be referred to as polyostotic FD.[5]

As reported previously in the literature, only the polyostotic form of FD may be associated

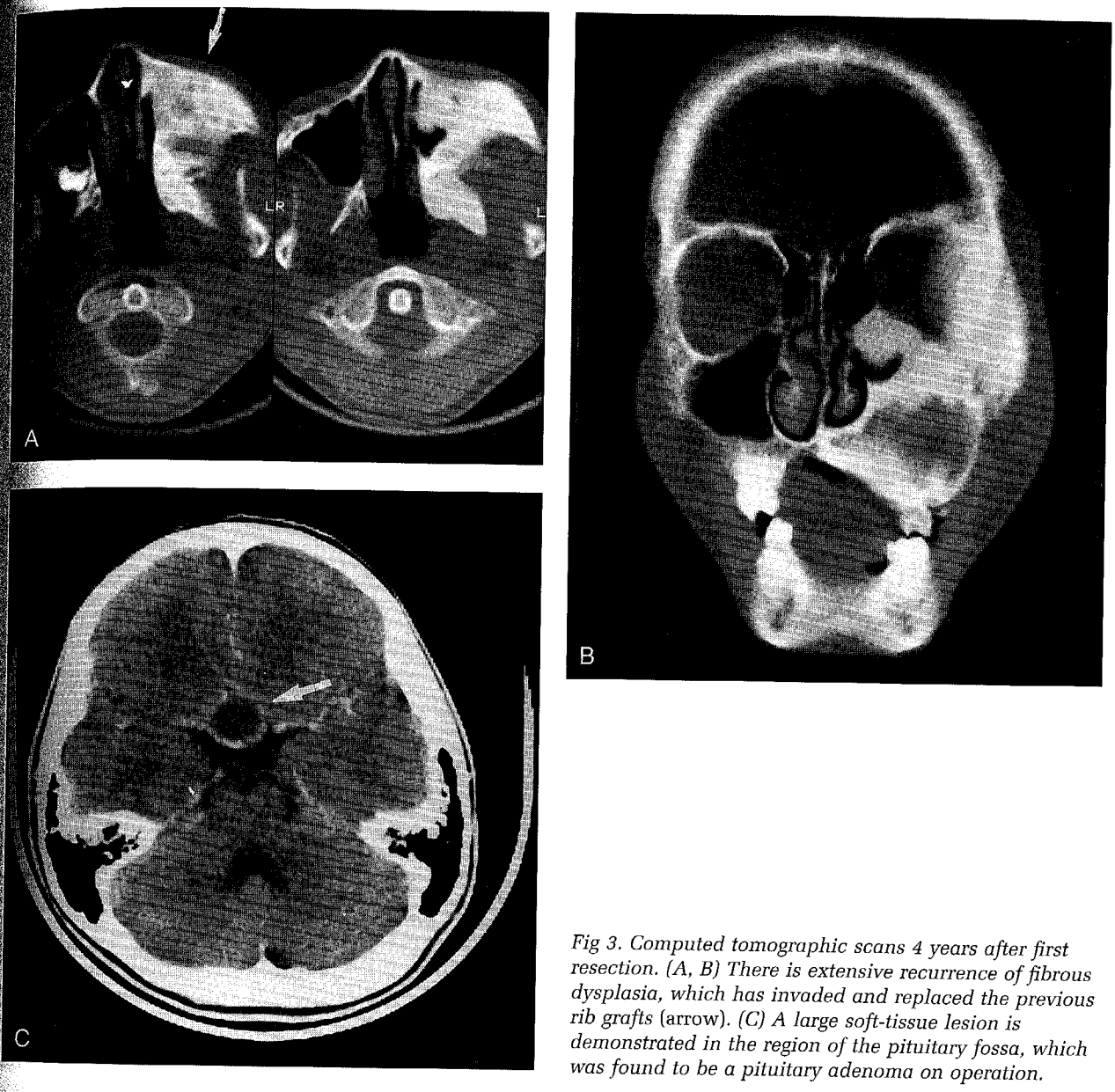

Fig 3. Computed tomographic scans 4 years after first resection. (A, B) There is extensive recurrence of fibrous dysplasia, which has invaded and replaced the previous rib grafts (arrow). *(C) A large soft-tissue lesion is demonstrated in the region of the pituitary fossa, which was found to be a pituitary adenoma on operation.*

with hormonal abnormalities. The classic description of what has become known as McCune-Albright syndrome includes polyostotic FD, precocious puberty in females, pigmented skin lesions, and short stature.[2,3,6] Other reports of hormonal abnormalities include hyperthyroidism, hyperparathyroidism, hypercortisolism, elevated prolactin, and disturbances in gonadal hormone levels. Adenomas and hyperplasias of the pituitary, thyroid, parathyroid, and adrenals as well as ovarian cysts have been found.[6] There are also more recent reports that the syndrome may involve more extensive organ systems, such as the heart, liver and thymus, and may even result in sudden death.[3,7]

The association of juvenile gigantism with polyostotic FD was first reported in 1942.[1] Excess growth hormone from a pituitary adenoma has been proposed to explain both the enormous height and huge fibrous dysplastic craniofacial bony enlargement of the "Tegernsee giant" mentioned previously.[2] Of all the hormonal abnormalities described in McCune-Albright syndrome, elevated growth hormone associated with juvenile gigantism may be the least common. Until 1991, a review of the literature reported only 26 patients.[8] Since that time, additional patient reports have appeared.[3,9–16] In all patients, the polyostotic form of FD was present. Polyostotic FD associ-

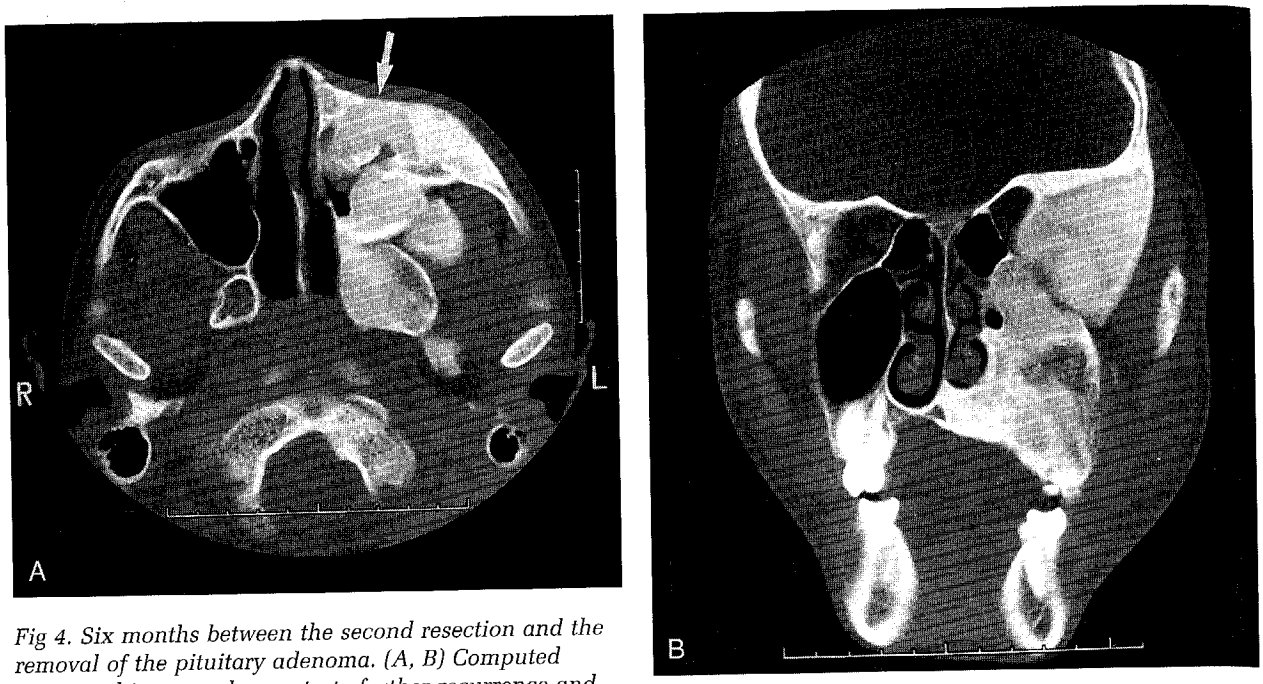

Fig 4. Six months between the second resection and the removal of the pituitary adenoma. (A, B) Computed tomographic scans demonstrate further recurrence and expansion of the remaining rib grafts by fibrous dysplasia (arrow).

ated with growth hormone and prolactin excess is thought to be even more uncommon.[12] The additional association of male gender is the most rare.[17] Although McCune-Albright syndrome usually includes short stature secondary to premature epiphyseal closure, the influence of excess growth hormone in many reported patients[2,7,12,18] may produce gigantism.

The aggressive recurrence and invasion of a previously radically resected and bone-grafted site stimulates discussion of both etiology and surgical strategy in FD. We propose that our patient's unusual clinical course of FD was due to the influence of the excessive production of growth hormone by the pituitary tumor. There are many reports in the literature to support this contention. Albright was the first to suggest that hormonal excess influenced bony lesion growth in FD.[19] Reactivation of FD after years of quiescence by endocrine tumors has been seen in polyostotic FD,[20] and is being particularly extensive and aggressive when associated with growth hormone excess.[21]

The hormonal effects of pregnancy have been suggested to stimulate FD,[22,23] and increased concentrations of estrogen receptors have been found in the fibrous dyplastic bone of McCune-Albright patients.[24] FD has been reported to have developed in an adult woman 24 years after premature menarche.[25] These observations have led to the proposition that FD does not "burn out" with adulthood,[23,26] but rather it slows down and becomes quiescent after the effects of pubertal hormones subside to adult levels.

Recently a postzygotic mutation in the gene coding for the guanine nucleotide binding regulatory protein of adenyl cyclase has been identified in McCune-Albright patients.[3] The resultant activation of the hormonally sensitive adenyl cyclase system may permit increased stimulation from excess secreted by a pituitary tumor. Thus FD may result from the interplay of hormonal excess acting on a genetically sensitized bone. Furthermore, the proposed mosaicism (postzygotic mutation) may be able to explain the variable and segmental distribution of select skin, endocrine, and bony sites.[3,6,25] This gene mutation has also been reported recently in a patient with monostotic FD in a non-McCune-Albright patient.[7] This suggests that monostotic FD, polyostotic FD without endocrine involvement, and the McCune-Albright syndrome may be variable expressions of the same spectrum.

Although the previous discussion provides

compelling support that growth hormone excess may stimulate FD lesion growth, there is no direct evidence for this contention. Further questions arise. First, is the elevated level of growth hormone predominantly responsible for our patient's aggressive recurrence, or is there an inherent predisposition of FD bony sites in this patient? Second, is the aggressive nature of some FD patients without a measurable endocrine excess due to a yet unknown stimulatory substance or simply due to higher concentrations of mutated cells at a particular site?

Surgical options in craniofacial FD include conservative recontouring, subradical resection with or without bone graft reconstruction, and radical or near total resection with primary bone graft reconstruction.[4,27–29] Although there are proponents for both ends of the management scale, it must also be remembered that surgical strategies in themselves also differ when dealing with varying aggressiveness of FD as well as the site or sites involved.

Resection after the pubertal growth spurt has been recommended in slowly progressive forms of FD. It is clear from a review of our patients, and from that of others, that conservative "shaving" can often give adequate and sometimes lasting aesthetic results in most patients with typical and slowly progressive forms of FD. This should be tempered, however, with the understanding that in all patients there may be at least some recurrence.

The rapidity of recurrence is variable and unpredictable. In those patients in whom recurrence causes unacceptable facial deformity, reoperative "shaving" can be performed, quite often with acceptable results. However, when FD growth is early, aggressive, and involves vital structures such as the optic canal, early surgical intervention has been proposed.[2,27–29]

The previous proposition that a postzygotic mutational mosaicism in selected skin, endocrine, and bony sites may inherently predispose these sites to hormonal activation suggests that total or complete resection may have prevented recurrence in this patient by not only removing obviously dysplastic bone, but also by including adjacent genetically predisposed tissue. While the proposal for complete resection of inherently predisposed fibrous dysplastic bony sites is theoretically attractive, there are many problems with this approach. Firstly, most patients who have hormonal excess or aggressive forms of FD have extensive disease that often involves unresectable sites at the time of diagnosis. Secondly, the border between healthy and afflicted bone is often difficult to differentiate at the time of surgery. Lastly, recurrences have been reported in contiguous sites not previously known to be involved with FD during the first resection. Therefore, it is clear that in most patients only radical or near-total resection can be achieved in extensive craniofacial disease.

The question of alternative therapy or combined therapy is then raised. Our patient was placed on Sandostatin for temporary control of growth hormone excess prior to the planned neurosurgical pituitary adenomatous resection. Hormonal treatment to alleviate the symptoms and progression of acromegaly has been used in many patients.[5] If one accepts that FD is in part a product of hormonal excess, this treatment therefore would also be expected to improve the bony lesions. A study of the long-term effects of pamidronate and etidronate in patients with FD found this hormonal manipulation to be of benefit in decreasing bone pain, radiologically improving bone lesions, and decreasing bone turnover.[30] Further investigation of possible hormonal manipulation of the bony lesions in FD is therefore warranted.

Summary

Presented is a patient with juvenile gigantism and growth hormone excess, similar to that of the "Tegernsee giant" and other more recently reported patients. We propose that the aggressive recurrence and unusual invasion of the radically resected and bone graft reconstruction site is due to the excessive production of growth hormone by the associated pituitary adenoma. This is supported by our clinical, radiological, and histological evidence, and is indirectly supported by evidence from the literature. Because of extensive involvement of unresectable structures at the time of diagnosis, the suggestion of combined surgical and hormonal management in these un-

usually aggressive forms of craniofacial FD warrants further investigation.

References

1 Wrong O. Tegernsee giant. Lancet 1992;339:194
2 Vogl TJ, Nerlich A, Dresel S, et al. CT of the 'Tegernsee giant': juvenile gigantism and polyostotic fibrous dysplasia. J Comput Assist Tomogr 1994;18:319–322
3 Shenker A, Weinstein LS, Moran A, et al. Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein Gs. J Pediatr 1993;123:509–518
4 Chen YR, Noordhoff MS. Treatment of craniomaxillofacial fibrous dysplasia: how extensive and how aggressive? Plast Reconstr Surg 1990;86:835–842
5 Edgerton MT, Persing JA, Jane JA. The surgical treatment of fibrous dysplasia. Ann Surg 1985;202:459–478
6 Nakagawa H, Hagasaka A, Sugiura T, et al. Gigantism associated with McCune-Albright's syndrome. Horm Metab Res 1985;17:522–527
7 Shenker A, Chanson P, Weinstein LS, et al. Osteoblastic cells from monostotic fibrous dysplasia contain Arg201 mutation of Gs-alpha mutation. J Bone Miner Res 1993;8: S139
8 Chiba Y, Tani N, Tamura N, et al. A case of fibrous dysplasia (McCune-Albright syndrome) associated with acromegaly (English abstract). Nippon Naibunpi Gakkai Zasshi 1991;67:239–248
9 Chanson P, Dib A, Visot A, et al. McCune-Albright syndrome and acromegaly: clinical studies and responses to treatment in five cases. Eur J Endocrinol 1994;131:229–234
10 Huang TS, Chang CC, Huang JS, et al. Albright's syndrome with acromegaly and Hashimoto's thyroiditis: report of a case. J Formos Med Assoc 1990;89:714–718
11 Abs R, Beckers A, Van de Vyver FL, et al. Acromegaly, multinodular goiter and silent polyostotic fibrous dysplasia. A variant of the McCune-Albright syndrome. J Endocrinol Invest 1990;13:671–675
12 Cremonini N, Graziano E, Chiarini V, et al. Atypical McCune-Albright's syndrome associated with growth hormone-prolactin pituitary adenoma: natural history, long term follow-up, and SMS 201-995-bromocryptine combined treatment results. J Clin Endocrinol Metab 1992;75: 1166–1169
13 Daly BD, Chow CC, Cockram CS. Unusual manifestations of craniofacial fibrous dysplasia: clinical, endocrinological and computed tomographic features. Postgrad Med J 1994;70:10–16
14 Kupcha PC, Guille JT, Tassanawipas A, et al. Polyostotic fibrous dysplasia and acromegaly (review). J Pediatr Orthop 1991;11:95–99
15 Premawardhana LD, Vora JP, Mills R, et al. Acromegaly and its treatment in the McCune Albright syndrome. Clin Endocrinol 1992;336:605–608
16 Vukovic D, Katanic D, Parric V, et al. The McCune-Albright syndrome with hyperthyroidism, acromegaly and hypophosphatemic-hyperphosphaturic rickets (English abstract). Med Pregl 1990;43:301–304
17 Harris RI. Polyostotic fibrous dysplasia with acromegaly. Am J Med 1985;78:539–542
18 Lightner ES, Penny R, Fraiser SD. Growth hormone excess and sexual precocity in polyostotic fibrous dysplasia (McCune-Albright syndrome): evidence for abnormal hypothalamic function. J Pediatr 1975;87:922–927
19 Albin J, Wu R. Abnormal hypothalamic pituitary function in polyostotic fibrous dysplasia. Clin Endocrinol 1981;14: 435–443
20 Hall MB, Sclar AG, Gardner DF. Albright's syndrome with reactivation of fibrous dysplasia secondary to pituitary adenoma and further complicated by osteogenic sarcoma: report of a case. Oral Surg 1984;57:616–619
21 Kovacs K, Horvath E, Thorner MO, et al. Mammosomatotroph hyperplasia associated with acromegaly and hyperprolactinemia in a patient with the McCune-Albright syndrome. Virchows Archiv 1984;403:77–86
22 Okudera H, Toba Y, Kyoshima K, et al. Monostotic fibrous dysplasia of the sphenoid bone presenting with visual disturbance during pregnancy (English abstract). No To Shinkei 1998;40:727–732
23 Davies ML, Macpherson P. Fibrous dysplasia of the skull: disease activity in relation to age. Br J Radiol 1991;64: 576–579
24 Kaplan FS, Fallon MD, Boden SD, et al. Estrogen receptors in bone in a patient with polyostotic fibrous dysplasia (McCune-Albright syndrome). N Engl J Med 1998;319: 421–425
25 Malchoff CD, Reardon G, MacBillivaray DC, et al. An unusual presentation of McCune-Albright syndrome confirmed by an activating mutation of the Gs alpha-subunit from a bone lesion. J Clin Endocrinol Metab 1994;78:803–806
26 Nager GT, Kennedy DW, Kopstein E. Fibrous dysplasia: a review of the disease and its manifestations in the temporal bone. Ann Otol Rhinol Laryngol 1982;92(Suppl):1–52
27 Munro IR, Chen YR. Radical treatment for fronto-orbital fibrous dysplasia: the chain link fence. Plast Reconstr Surg 1981;67:719–730
28 Jackson IT, Hide TAH, Gomuwka PK, et al. Treatment of cranio-orbital fibrous dysplasia. J Maxillofac Surg 1982; 10:138–141
29 Chen YR, Fairholm D. Fronto-orbital-sphenoidal fibrous dysplasia. Ann Plast Surg 1985;15:190–203
30 Liens D, Delmas PD, Meunier P. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. Lancet 1994;343:953–954